

AMENDMENTS TO THE SPECIFICATION:

All amendments to the specification refer to amendments to paragraph numbers of Publication No. 2005/0158295 ("the Publication").

Please replace paragraphs [0019], [0030], [0090], [0091], [0092] and [0209] of the Publication with the following rewritten paragraphs:

[0019] The three dimensional structure of the latent form of PAI 1 has been solved. In this structure the entire N terminal side of the reactive center loop is inserted as the central strand into β -sheet A (FIG. 6A) (Mottonen et al., supra) which explains the increased stability (Lawrence, D. A. et al., Biochemistry 33:3643 3648 (1994)) as well as the lack of inhibitory activity. It has been proposed that the reactive center in active PAI 1 is exposed as a surface loop, in contrast to its position in the latent structure (FIG. 6B).

[0030] FIGS. ~~4A-D~~ 1A-E. The nucleotide sequence (SEQ ID NO:1) encoding human PAI 1 plus 5' and 3' untranslated regions from a particular clone. Also shown is the amino acid sequence of full length human PAI 1 including the signal peptide (SEQ ID NO:2).

[0090] In one embodiment, one or more chemoagents are administered together or conjugated together with the modified PAI-1 molecules of the invention ("Therapeutics" of the present invention) to treat a cancer patient. A chemoagent (or "anti-cancer agent" or "anti-tumor agent" or "cancer therapeutic") refers to any molecule or compound that assists in the treatment of tumors or cancer. Examples of chemoagents include, but are not limited to, cytosine arabinoside, taxoids (e.g., paclitaxel, docetaxel), anti-tubulin agents (e.g., paclitaxel, docetaxel, epothilone B, or its analogues), macrolides (e.g., rhizoxin) cisplatin, carboplatin, adriamycin, tenoposide, mitozantron, discodermolide, eleutherobine, 2 chlorodeoxyadenosine, alkylating agents (e.g., cyclophosphamide, mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin, thio-tepa), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, anthramycin), antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, flavopiridol, 5-fluorouracil, fludarabine, gemcitabine, dacarbazine, temozolamide), asparaginase, Bacillus Calmette Guerin, diphtheria toxin, hexamethylmelamine, hydroxyurea, LYSODREN® (mitotane), nucleoside analogues,

plant alkaloids (e.g., Taxol, paclitaxel, camptothecin, topotecan, ~~irinotecan (CAMPTOSAR, CPT-11)~~, CAMPTOSAR®, CPT-11 (irinotecan)), vincristine, vinca alkyls such as vinblastine), podophyllotoxin (including derivatives such as epipodophyllotoxin, VP-16 (etoposide), VM-26 (teniposide)), cytochalasin B, colchicine, gramicidin D, ethidium bromide, emetine, mitomycin, procarbazine, mechlorethamine, anthracyclines (e.g., daunorubicin (formerly daunomycin), doxorubicin, doxorubicin liposomal), dihydroxyanthracindione, mitoxantrone, mithramycin, actinomycin D, procaine, tetracaine, lidocaine, propranolol, puromycin, anti-mitotic agents, abrin, ricin A, pseudomonas exotoxin, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, aldesleukin, allutamine, anastrozole, bicalutamide, biaomycin, busulfan, capecitabine, carboplatin, chlorabasil, cladribine, cytarabine, daclinomycin, estramustine, floxuridine, gemcitabine, gosereine, idarubicin, itosfamide, lauprolide acetate, levamisole, lomustine, mechlorethamine, megestrol, acetate, mercaptopurine, mesna, mitolanc, pegaspargase, pentostatin, picamycin, rituximab, campath-1, streptozocin, thioguanine, tretinoin, vinorelbine, or any fragments, family members, or derivatives thereof, including pharmaceutically acceptable salts thereof.

[0091] In other embodiments, the method for the treatment of cancers further comprises administration of pharmaceutical compositions comprising 5-fluorouracil, cisplatin, docetaxel, doxorubicin, ~~Herceptin®~~ HERCEPTIN® (trastuzumab), gemcitabine (Seidman, 2001, Oncology 15:11 14), IL-2, paclitaxel, and/or VP-16 (etoposide). In another embodiment, pharmaceutical compositions comprises modified PAI-1 molecules of the present invention conjugated with the above agents.

[0092] In another embodiment, the treatment of the present invention further includes the administration of one or more immunotherapeutic agents, such as antibodies and immunomodulators, which include, but are not limited to, HERCEPTIN® (trastuzumab), RITUXAN® (rituximab), OVAREX™ (oregovomab), PANOREX® (edrecolomab), BEC2, IMC-C225, VITAXIN™, CAMPATH® ~~1H~~ 1H (alemtuzumab), Smart MI95, LYMPHOCIDE™ (epratuzumab), Smart ID10, and ONCOLYM™ (1-131 LYM-1), rituximab, gemtuzumab, or trastuzumab.

[0209] Tris (50mM) with 0.01% Tween 80, 0.01% PEG 8000 (pH 8.8) and 10 KIU/ml sterile aprotinin (Sigma Chemical Co., St. Louis, MO) was incubated with 1µg of

uPA and decreasing amounts of inhibitor (initially 100 µg/ml) for 15 minutes; 100 µl of this mixture was incubated in 96-well microplates with 50µl of 2.5 mM ~~Spectozyme~~ SPECTROZYME® UK (Cbo-L-(γ)-Glu (α-t-BuO)-Gly-Arg-pNA.2AcOH), (American Diagnostica Inc., Greenwich, CT), for 15 mins. Absorbance at 405 nm was read on a microplate reader. Absorbance is inversely proportional to the uPA inhibitory activity.